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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NASHED, NASHAAT T	
ART UNIT	**PAPER NUMBER**
1652	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/740,313	Applicant(s) Khosla et al.
	Examiner Nashaat T. Nashed	Art Unit 1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 18, 2000*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-7 and 31-43* is/are pending in the application.

4a) Of the above, claim(s) *1-7* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *31-43* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *6 and 7*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

The application has been amended as requested in the communication filed December 18, 2000. Accordingly, claims 8-30 have been canceled, and new claims 31-43 have been entered.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group I Claims 1-7, drawn to a method of preparing a nucleotide sequence encoding a modified polyketide synthase (PKS), classified in Class 435, subclass 91.1+.

Group II Claims 31-43, drawn to a method of making polyketide analogs, classified in Class 435, subclass 76.

The inventions are distinct, each from the other because of the following reasons:

Inventions of Groups I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the different inventions are independent methods having different mode of operation and practicing the method yield different products.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with Kate H. Murashige on May 30, 2003 a provisional election was made with traverse to prosecute the invention of Group II, claims 31-43. Claims 1-7 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

Priority Date for the Claims in the Instant Application:

The instant application is a continuation of serial number 08/846,247, filed 4/30/97, now U. S. P. 6,391,594, which is CIP 08/486,645 filed 6/7/95, now U. S. P. 5,712,146, Which is a CIP of serial number 08/238,811, filed 5/6/94, now U. S. P. 5,672,491, which

is ..... *etc.* The instant claims are neither described or enabled in serial numbers 08/486,645 and 08/238,811. Enabled embodiment of the instant claims are found in serial numbers 08/846,247. Thus, the earliest priority date for the instant application is **not earlier than April 30, 1997**.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The method of claims 31-43 lacks antecedent basis in the specification.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 31-43 are directed to a method of directing the biosynthesis of a specific macrolide polyketide analog by deleting, inserting or substituting in a nucleic acid the coding region of an enzymatic activity by another from another module from the same gene cluster or from a different gene cluster. The specification, however, only provides two representative species in which catalytic domains of DEBS are replaced with similar catalytic domain from the gene cluster encoding rapamycin (RAP) and *visa versa* as well as well as disabling mutation of keto-modifying activity. The DEBS and the RAP gene clusters were the only known gene clusters encoding the biosynthetic pathways for polyketides at the time of invention, see the first paragraph of page 9. Among the genes that are reported in the specification to be mapped or partially sequenced, there is no teaching of a structure of any nucleic acid encoding any polypeptide synthase or any domains structures from any of them. There is no disclosure of any particular structure to function/activity relationship in the disclosed species. The specification also fails to describe additional representative species of these DNAs by any identifying structural

characteristics or properties other than the activities recited in claim 1, for which no predictability of structure is apparent. In particular, claims 42 and 43 are directed to a method wherein step 1 of the method of claim 34 involve a gene cluster selected from the group consisting of rapamycin, avermectin, FK-506, FR-008, monensin, rifamycin, sorphain-A, spinocyn, squalestatin, and tylosin. With the exception of the gene cluster of rapamycin, none of the other gene clusters are described in the specification. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claims 31-43 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to polyketide synthase of the DEBS and RAP gene clusters as a source of the PKS gene clusters and the nucleic acid encoding specific catalytic domains. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to a method of making any modified PKS from any biological source in which a catalytic domain is deleted, inserted or substituted by another from any other PKS gene cluster from any biological source. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses a method of modifying any polyketide synthase (PKS) by deleting, inserting and/or substituting a catalytic domain by another domain from any other PKS. The specification provides guidance and examples in the form of an assay to make a nucleic acid encoding modified PKS by deletion or substituting of catalytic domains in DEBS and RAP with another catalytic domains from DEBS or RAP (examples 1-5). While molecular biological techniques and genetic manipulation to make the constructs claimed are known in the prior art and the skill of the artisan are well developed, knowledge regarding the gene clusters or gene encoding polyketide synthases from any biological source and their genomic organization as well as the various catalytic domains in each of the polyketide synthases is lacking. Thus, searching for a gene cluster encoding any polyketide synthase, let alone a nucleic acid encoding a modified polyketide synthase in which a catalytic domain is modified by deletion, insertion or substitution with another catalytic domain from another polyketide synthase, is well outside the realm of routine experimentation and predictability in the art of success is extremely low. The amount of experimentation to identify a gene

cluster, identify the different open reading frames, and identify all the catalytic domains is enormous. Since routine experimentation in the art does not include screening vast numbers of genomic and cDNA libraries from various microorganisms where the expectation of obtaining the desired gene cluster is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the nucleic acid sequence of the gene clusters, the open reading frames, and the various catalytic domains in each open reading frame. Without such a guidance, the experimentation left to those skilled in the art is undue.

Claims 31-43 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

(a) The phrase "identifying enzymatic activity associated within said gene-containing DNA sequence" in claim 31 renders the claims indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. For examination purposes only, the phrase is taken to mean "identifying a coding region of an enzymatic activity within said gene-containing DNA sequence".

(b) Step (3) of claim 31 " introducing one or more specified changes into said gene-containing sequence" renders the claim confusing and indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Since step (3) does not restrict the changes to a specific part of the nucleic acid such as the coding sequence for the enzymatic activity identified in step (2), the changes could be either in coding region of the enzymatic activities, the scaffold regions or even the non-coding regions. For examination purposes only, step (3) is taken to mean "any changes to the nucleic acid of the gene cluster.

(c) The phrases "at least one region" in claim 34, and "one or more specified changes" in claims 31 and 34 render the claims indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. For examination purposes, the phrase is taken to mean disabling mutation of a catalytic domain/module, deletion of the catalytic domain/module, inserting a catalytic domain/module, and/or substitution of catalytic domain/module.

(b) Claims 32, 33, and 35-43 are included in this rejection because they are dependent on rejected claims and do not cure its deficiencies.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 31-43 are rejected under 35 U.S.C. § 102(b) as being anticipated by Katz *et al.* (Katz, IDS: reference 16, WO 93/13663).

Katz teach a method for obtaining novel polyketides by introducing specific changes in the DNA encoding the biosynthetic pathway of a polyketide, the summary of invention on page 2, the DNA sequence for the *eryA* gene cluster and the amino acid sequences of the three open reading frame encoded thereby, see Figure 2, and exemplify the changes in the *eryA* gene cluster (also known as DEBS). Figure 1 describes the various enzymatic activities in each open reading frame. Also, they teach that the extender unit employed at each condensation is specified by the acyltransferase function determined by each module, see page 6, lines 26-29, and the production of polyketide in microorganisms producing polyketide such as *Saccharapolyspora erythrea*, *Streptomyces antibioticusl*, *S. hygroscopicus* and *S. venezuelae* among others, see page 4, last paragraph. The method taught by Katz encompasses transforming a polyketide producing microorganism with the modified nucleic acid and culturing the microorganism and harvesting the product polyketide. The instant claims are directed to a method for modifying a nucleic acid sequence encoding an enzymatic activity in a modular polyketide synthase, said modification include disabling an enzymatic activity, deleting a coding sequence for an enzymatic activity, inserting a coding sequence for enzymatic activity and/or substituting a coding sequence for an enzymatic activity by another coding sequence for similar enzymatic activity, modification described by Katz as type I-III changes, see page 7, lines 12-18. Said nucleic acid changes comprise three types: (i) Type I change produces macrolide having the same ring size, but it has different functional group(s) at specific ring position, (ii) Type II Change produces macrolide rings only when fed exogenous substrates and their analogs, and (iii) type III change would be expected to produce a change in the macrolide ring size. Independent claims 31 and 34 of the instant application are either identical or slightly modified version of claim 1 in Katz. Claims 32, and 35-37 of the instant application correspond to claims 20, 23, 24, and 26 of Katz. Also, claim 33 of the instant application corresponds to claim 28 and 29 of Katz. In addition, claims 38 and 39 correspond to claim 14, 9, and 16 of Katz. Specifically, Katz exemplify each of the

changes described as Type I-III in examples 1-44 using the *eryA* gene cluster (claims 31-41). In addition, Katz teach that the method is applicable to any gene cluster including those encoding the biosynthetic pathway of rapamycin, avermectin, FK-506, and tylosin (claims 42 and 43), see pages 31-37.

Claims 31-43 are rejected under 35 U.S.C. § 102(e) as being anticipated by U. S. P 5,824,513 (513).

The 513 patent appear to be identical to Katz (WO 93/13663). It teaches a method for obtaining novel polyketides by introducing specific changes in the DNA encoding the biosynthetic pathway of a polyketide, the summary of invention, the paragraph bridging columns 1 and 2, the DNA sequence for the *eryA* gene cluster and the amino acid sequences of the three open reading frame encoded thereby, see Figure 2, and exemplify the changes in the *eryA* gene cluster (also known as DEBS). Figure 1 describes the various enzymatic activities in each open reading frame. Also, they teach that the extender unit employed at each condensation is specified by the acyltransferase function determined by each module, see page 6, lines 26-29, and the production of polyketide in microorganisms producing polyketide such as *Saccharapolyspora erythrea*, *Streptomyces antibioticusl*, *S. hygroscopicus* and *S. venezuelae* among others, see page 4, last paragraph. The method taught by in the 513 patent encompasses transforming a polyketide producing microorganism with the modified nucleic acid and culturing the microorganism and harvesting the product polyketide. The instant claims are directed to a method for modifying a nucleic acid sequence encoding an enzymatic activity in a modular polyketide synthase, said modification include disabling an enzymatic activity, deleting a coding sequence for an enzymatic activity, inserting a coding sequence for enzymatic activity and/or substituting a coding sequence for an enzymatic activity by another coding sequence for similar enzymatic activity, modification described by in the 513 patent as type I-III changes, see page 7, lines 12-18. The nucleic acid changes described in the 513 patent include: (i) Type I change produces macrolide having the same ring size, but it has different functional group(s) at specific ring position, (ii) Type II Change produces macrolide rings only when fed exogenous substrates and their analogs, and (iii) type III change would be expected to produce a change in the macrolide ring size. Independent claims 31 and 34 of the instant application are broader in scope than claim 1 of 513 patent. Claim 1 of the 513 patent is limited to *eryA* gene cluster. Also, the other dependent claims 32, 33 and 35-43 of the instant application are very similar to some of the dependent claims 2-18. Specifically, the 513 patent exemplifies each of the changes described as types I-III in examples 1-44 using the *eryA* gene cluster (claims 31-41). In addition, the 513 patent teaches that the method is applicable to any gene cluster including those encoding the biosynthetic pathway of rapamycin, avermectin, FK-506, and tylosin (claims 42 and 43), see from line 48, column 20 through column 26, line 19.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is (703) 305-6586. The examiner can normally be reached Monday, Tuesday, Thursday, and Friday from 9:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (703) 308-3804. The fax phone numbers for this Group are (703) 305-3014 and (703)308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Nashaat T. Nashed, Ph. D.
Primary Examiner